CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 018948/S016

Trade Name: CARNITOR TABLETS

Generic Name: LEVOCARNITINE

Sponsor: SIGMA-TAU PHARMACEUTICALS, INC.

Approval Date: 07/14/92

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 018948/S016

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Chemistry Review(s)	X			
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Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)				
Administrative Document(s)				
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 018948/S016

APPROVAL LETTER

JUL 14 1992

NDA 18-948/S-016

Sigma-Tau Pharmaceuticals, Inc.
Attention: Edward D. Helton, Ph.D.
Director, Research and Regulatory Affairs
200 Orchard Ridge Drive
Gaithersburg, MD 20878

Dear Dr. Helton:

Reference is made to your supplemental new drug application dated June 30, 1992, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Carnitor (levocarnitine) Tablets.

The supplement provides for

We have completed our review of this supplemental application, along with final printed labeling, and it is approved, effective on the date of this letter.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

/S/

APPEARS THIS WAY
ON ORIGINAL

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research

cc: NDA Arch.
HFD-510
HFC-130/JAllen
HFD-80/labelling attached
HFD-500/LRipper/labelling attached
HFD-638/labelling attached
HFD-735/labelling attached
HFD-510/DWu/YYChiu
HFD-511/LBraithwaite for SOlmstead/07.13.92/N18948AP.S16/ft/nls/7/13/92

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ON ORIGINAL

Concurrence: DWu, YYChiu, 7.13.92

SUPPLEMENT APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 018948/S016

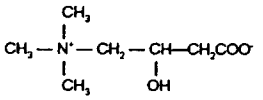
FINAL PRINTED LABELING

CARNITOR®

(Levocarnitine)

CARNITOR® (Levocarnitine) Tablets (330 mg)
CARNITOR® (Levocarnitine) Oral Solution
(1 g per 10 mL multidose)
For oral use only. **Not for parenteral use.**

Description
CARNITOR® (Levocarnitine) is L-beta-hydroxy-gamma-trimethylamino butyric acid (inner salt). As a bulk drug substance it is a white powder with a melting point of 196-197° C and is readily soluble in water. The L-isomer of carnitine is the biologically active form. Its chemical structure is:



Each CARNITOR® (Levocarnitine) Tablet contains 330 mg of levocarnitine and the inactive ingredients magnesium stearate, microcrystalline cellulose and povidone.
Each 118 mL container of the CARNITOR® (Levocarnitine) Oral Solution contains 1 g of levocarnitine/10 mL, sucrose syrup, D,L-malic acid, red colors and artificial cherry flavor. Methyl paraben NF and Propylparaben NF are added as preservatives. The pH is approximately 5.

Clinical pharmacology
CARNITOR® (Levocarnitine) is a naturally occurring substance required in mammalian energy metabolism. It has been shown to facilitate long-chain fatty acid entry into cellular mitochondria, therefore delivering substrate for oxidation and subsequent energy production. Fatty acids are utilized as an energy substrate in all tissues except the brain. In skeletal and cardiac muscle they serve as major fuel. Primary systemic carnitine deficiency is characterized by low plasma, RBC, and/or tissue levels. The resulting impairment in fatty acid metabolism manifests itself as elevated triglycerides and free fatty acids, diminished ketogenesis, and lipid infiltration of liver and muscle. The literature reports that carnitine can promote the excretion of excess organic or fatty acids in patients with defects in fatty acid metabolism and/or specific organic acidopathies that bioaccumulate acylCoA esters.

Bioavailability
The bioavailability/pharmacokinetics of CARNITOR® (Levocarnitine) Tablets and the Oral Solution presentation have not been determined in well controlled studies.

Metabolism and excretion
The majority of body carnitine is excreted in the urine and feces. In renal failure, carnitine levels may rise.

Indications and usage
CARNITOR® (Levocarnitine) is indicated in the treatment of primary systemic carnitine deficiency. In the reported cases, the clinical presentation consisted of recurrent episodes of Reye-like encephalopathy, hypoketotic hypoglycemia, and/or cardiomyopathy. Associated symptoms included hypotonia, muscle weakness and failure to thrive. A diagnosis of primary carnitine deficiency requires that serum, red cell and/or tissue carnitine levels be low and that the patient does not have a primary defect in fatty acid or organic acid oxidation (see Clinical Pharmacology). Controlled trials were not conducted, but in some patients, particularly those presenting with cardiomyopathy, carnitine supplementation rapidly alleviated signs and symptoms. Treatment should include, in addition to carnitine, supportive and other therapy as indicated by the condition of the patient.

Contraindications
None known.

Warnings
None.

Precautions
General
CARNITOR® (Levocarnitine) Oral Solution is for oral/internal use only.
Not for parenteral use.
Gastrointestinal reactions may result from too rapid consumption of carnitine. CARNITOR® (Levocarnitine) Oral Solution may be consumed alone, or dissolved in drinks or other liquid foods to reduce taste fatigue. It should be consumedslowly and doses should be spaced evenly throughout the day to maximize tolerance.

Carcinogenesis, mutagenesis, impairment of fertility
Mutagenicity tests have been performed in Salmonella typhimurium, Saccharomyces cerevisiae, and Schizosaccharomyces pombe that do not indicate that CARNITOR® (Levocarnitine) is mutagenic. Long-term animal studies have not been conducted to evaluate the carcinogenicity of the compound.

Usage in pregnancy
Pregnancy Category B Reproductive studies have been performed in rats and rabbits using parenteral administration at doses equivalent on a mg/kg basis to the suggested oral adult dosage and have revealed no harm to the fetus due to CARNITOR® (Levocarnitine). There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing mothers
Levocarnitine is a normal component of human milk. Levocarnitine supplementation in nursing mothers has not been studied.

Pediatric use
See Dosage and Administration

APPROVED 7-14-92

Adverse reactions
Various mild gastrointestinal complaints have been reported during the long-term administration of oral L- or D,L-carnitine; these include transient nausea and vomiting, abdominal cramps, and diarrhea. Mild myasthenia has been described only in uremic patients receiving D,L-carnitine. Gastrointestinal adverse reactions with CARNITOR® (Levocarnitine) Oral Solution dissolved in liquids might be avoided by a slow consumption of the solution or by a greater dilution. Decreasing the dosage often diminishes or eliminates drug-related patient body odor or gastrointestinal symptoms when present. Tolerance should be monitored very closely during the first week of administration, and after any dosage increases.

Overdosage
There have been no reports of toxicity from carnitine overdosage. The oral LD_{50} of levocarnitine in mice is 19.2 g/kg. Carnitine may cause diarrhea. Overdosage should be treated with supportive care.

Dosage and administration

CARNITOR® (Levocarnitine) Tablets.

Adults: The recommended oral dosage for adults is 990 mg two or three times a day using the 330 mg tablets, depending on clinical response.

Infants and children: The recommended oral dosage for infants and children is between 50 and 100 mg/kg/day in divided doses, with a maximum of 3 g/day. Dosage should begin at 50 mg/kg/day. The exact dosage will depend on clinical response.
Monitoring should include periodic blood chemistries, vital signs, plasma carnitine concentrations and overall clinical condition.

CARNITOR® (Levocarnitine) Oral Solution.

For oral use only. **Not for parenteral use.**

Adults: The recommended dosage of levocarnitine is 1 to 3 g/day for a 50 kg subject which is equivalent to 10 to 30 mL/day of Carnitor® (Levocarnitine) Oral Solution. Higher doses should be administered only with caution and only where clinical and biochemical considerations make it seem likely that higher doses will be of benefit. Dosage should start at 1 g/day, (10 mL/day), and be increased slowly while assessing tolerance and therapeutic response. Monitoring should include periodic blood chemistries, vital signs, plasma carnitine concentrations, and overall clinical condition.

Infants and children: The recommended dosage of levocarnitine is 50 to 100 mg/kg/day which is equivalent to 0.5 mL/kg/day CARNITOR® (Levocarnitine) Oral Solution. Higher doses should be administered only with caution and only where clinical and biochemical considerations make it seem likely that higher doses will be of benefit. Dosage should start at 50 mg/kg/day, and be increased slowly to a maximum of 3 g/day (30 mL/day) while assessing tolerance and therapeutic response. Monitoring should include periodic blood chemistries, vital signs, plasma carnitine concentrations, and overall clinical condition.
CARNITOR® (Levocarnitine) Oral Solution may be consumed alone or dissolved in drink or other liquid food. Doses should be spaced evenly throughout the day (every three or four hours) preferably during or following meals and should be consumed slowly in order to maximize tolerance.

How supplied
CARNITOR® (Levocarnitine) Tablets are supplied as 330 mg, individually foil wrapped tablets in boxes of 90 (NDC 54482-144-07). Store at room temperature (25°C / 77°F).
CARNITOR® (Levocarnitine) Oral Solution is supplied in 118 mL (4 FL. OZ.) multiple-unit plastic containers. The multiple-unit containers are packaged 24 per case (NDC 54482-145-08). Store at room temperature (25°C / 77°F).

Caution
Federal (U.S.A.) law prohibits dispensing without prescription.
CARNITOR® (Levocarnitine) Oral Solution manufactured for: Sigma-Tau Pharmaceuticals, Inc. By: Barre-National, Inc. Baltimore, MD 21207-2642

References
1. Bohmer T, Rynding A, Solberg HE: Carnitine levels in human serum in health and disease. Clin Chim Acta 57:55-61, 1974.
2. Brooks H, Goldberg L, Holland R et al: Carnitine-induced effects on cardiac and peripheral hemodynamics. J Clin Pharmacol 17:561-578, 1977.
3. Christiansen R, Bremer J: Active transport of butyrobetaine and carnitine into isolated liver cells. Biochem Biophys Acta 448:562-577, 1977.
4. Lindstedt S, Lindstedt G: Distribution and excretion of carnitine $^{14}CO_2$ in the rat. Acta Chim Scand 15:701-702, 1961.
5. Rebouche CJ, Engel AG: Carnitine metabolism and deficiency syndromes. Mayo Clin Proc 58:533-540, 1983.
6. Rebouche CJ, Paulson DJ: Carnitine metabolism and function in humans. Ann Rev Nutr 6:41-68, 1986.

sigma-tau
PHARMACEUTICALS, INC.
200 Orchard Ridge Drive, Gaithersburg, MD 20878

PREVIOUS EDITION IS OBSOLETE
ST-N18-948-3/92

APPROVED 7-14-92

Labeling: _____

NDA No: _____ Rec'd. _____

Reviewed by: _____

APPEARS THIS WAY
ON ORIGINAL

NDC 54482-145-08

118 mL (4 fl. oz.)
Multiple-Unit Container

Carnitor®

(Levocarnitine Oral Solution)

Contains L-carnitine 1 gm/10mL; sucrose syrup; D, L-malic acid, Methylparaben NF; Propylparaben NF; red colors and artificial cherry flavor

Manufactured for

SIGMA-TAU PHARMACEUTICALS, INC.
200 Orchard Ridge Drive
Gaithersburg, MD 20878

by: Barre-National, Inc.
7205 Windsor Boulevard
Baltimore, MD 21207-2642

Lot #03772
Exp. Date: 2/93

Dosage: As directed by physician.
avoid excess heat. Protect from freezing.
Store at room temperature (25°C).

Caution: Federal law prohibits dispensing without prescription.

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ON ORIGINAL

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ON ORIGINAL

NDC 54482-145-08

118 mL (4 fl. oz.)
Multiple-Unit Container

Carnitor®

(Levocarnitine Oral Solution)

Contains L-carnitine 1 gm/10 mL; sucrose syrup; D, L-malic acid; Methylparaben NF; Propylparaben NF; red colors and artificial cherry flavor.

Manufactured for:

SIGMA-TAU PHARMACEUTICALS, INC.
200 Orchard Ridge Drive
Gaithersburg, MD 20878

by: Barre-National, Inc.
7205 Windsor Boulevard
Baltimore, MD 21207-2642

Dosage: As directed by physician.
Avoid excess heat. Protect from freezing.
Store at room temperature (25°C).

Caution: Federal law prohibits dispensing without prescription.

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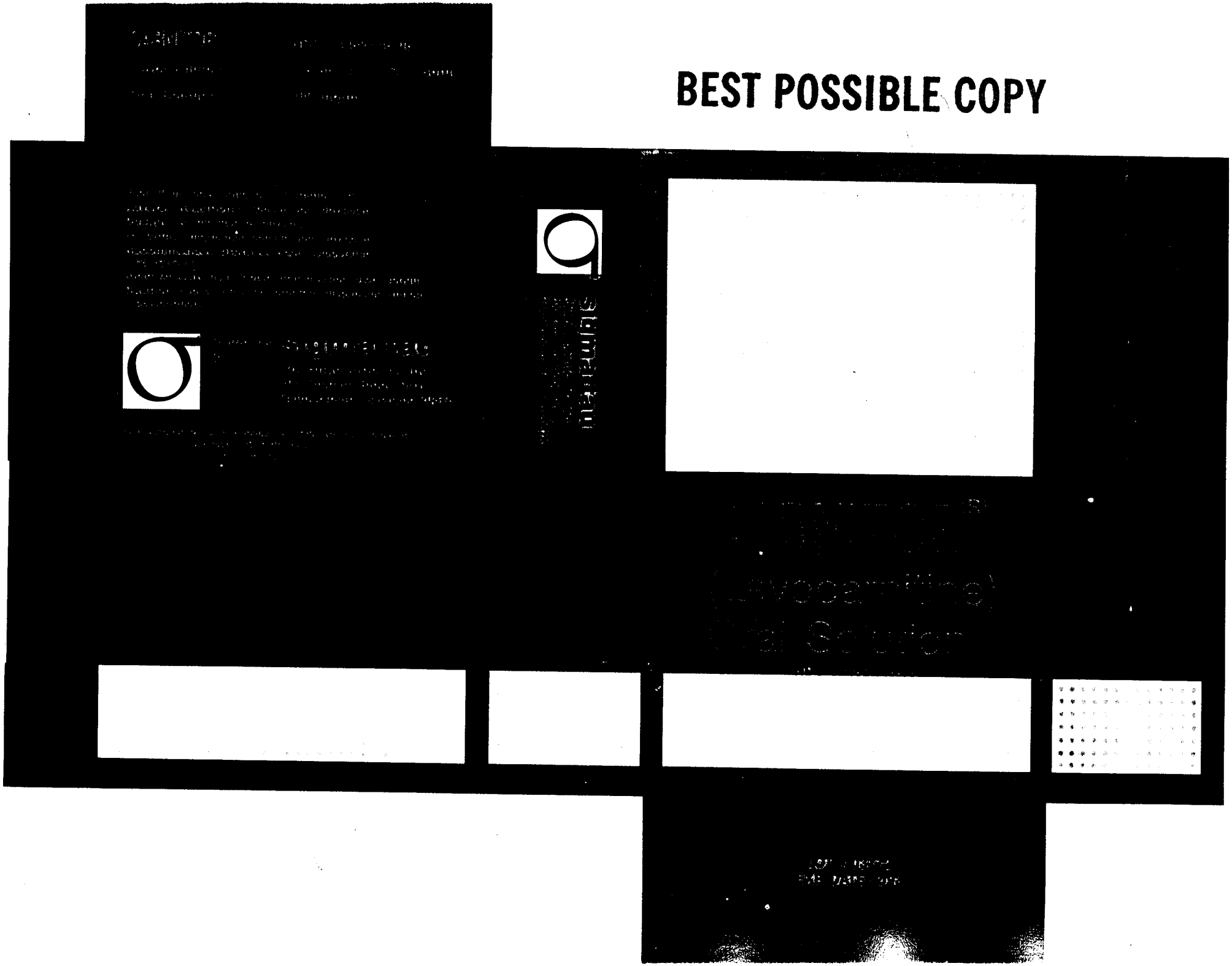

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 018948/S016

CHEMISTRY REVIEW(S)

ORIGINAL

JUL 10 1992

CHEMIST'S REVIEW	1. ORGANIZATION DMEDP, HFD-510	2. NDA NUMBER 18-948

3. NAME AND ADDRESS OF APPLICANT

Sigma-Tau Pharmaceuticals, Inc.
200 Ochard ridge Drive
Gaithers burg, Maryland 20878

4. SUPPLEMENTS/NUMBER, DATE

Supplement
S-016
6/30/92

6. NAME OF THE DRUG

Carnitor Tablets and
Oral Solution

7. NONPROPRIETARY NAME

Levocarnitine

9. AMENDMENTS/REPORTS, DATE

8. SUPPLEMENT PROVIDES FOR:

Sigma-Tau's Carnitor

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF
Treatment of carnitine deficiency	Oral	

13. DOSAGE FORM	14. POTENCY
Tablets and Oral Solution	330 mg, 1g/10mL

15. CHEMICAL NAME AND STRUCTURE

$C_7H_{15}NO_3$, Mol. Wt. 161.2

α-Hydroxy-γ-trimethylamino butyric acid

16. COMMENTS

17. CONCLUSIONS AND RECOMMENDATIONS

Information provided are satisfactory. The supplement should be approved.
Issue approval letter without delay.

18. NAME	REVIEWER SIGNATURE	DATE COMPLETED
Duu-Gong Wu, Ph.D.	/S/	7/10/92

DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE

R/D initialed by: /S/ 7/10/92

File name: 18948.s16

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 018948/S016

CORRESPONDENCE

sigma-tau

PHARMACEUTICALS, Inc.

200 orchard ridge drive, gaithersburg
maryland 20878

telephone: (301) 948.1041

telefax:
sales & marketing (301) 948.1862
scientific affairs (301) 948.8627

ORIGINAL

Labeling: [illegible]
NDA No: 18-948 Rec'd. 6/30/92
Reviewed by: _____

June 30, 1992

Solomon Sobel, M.D.
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)
Attention: DOCUMENT CONTROL ROOM 14B03
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

REVIEWS COMPLETED
CSO ACTION:
☑ LETTER ☐ N.A.I.
CSO INITIALS DATE

Re: NDA 18-948
Supplement: Relabel of Levocarnitine Oral Solution (Expedited Review)

Dear Dr. Sobel:

Please refer to our New Drug Application (NDA) for Carnitor® (levocarnitine) Tablets and Oral Solution submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.
In connection with Sigma-Tau

The supplement provides for

During a meeting (February 27, 1992) at the Parklawn Building, Mr. Helmut Nunn, Sigma-Tau Representative, discussed with Dr. Y.Y. Chiu and Dr. Duu-Gong Wu. Dr. Chiu was informed of the urgency of the review because the lot in question was going to expire at the end of February 1993. Dr. Chiu agreed to an expedited review.

Enclosed are 12 copies of the final printed over-lay labels and twelve cartons with the printed lot number and expiration date. We also enclose twelve copies of the currently approved bottle labels and package insert. There are no changes in the text.

Respectfully,

APPEARS THIS WAY
ON ORIGINAL

Edward D. Helton, Ph.D.
Director, Research and Regulatory Affairs

EH:eh

encls.

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